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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,375	12/08/2003	Philip J. Barr	39042-0014	4368

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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
04/14/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,375	BARR ET AL.	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,8,11 and 13-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,8,11 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The response filed January 8, 2008 have been received and entered into the application.

Action Summary

The rejection of claims 5, 8, 11, 13 and 15-20 under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) in view of Lezdey et al. (U.S.Patent No. 6,174,859 B1) is being maintained for the reasons stated in the previous Office Action.

The rejection of claims 14, 20 and 21 under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) in view of Lezdey et al. (U.S.Patent No. 6,174,859 B1) as applied to claims 5, 8, 11 and 13 above, and further in view of Brake et al. (U.S.Patent No. 4,752,576) is being maintained for the reasons stated in the previous Office Action.

Response to Arguments

Applicants' arguments filed January 8, 2008 have been fully considered but they are not persuasive. Applicants argue that Avidano et al. discloses results for *in vitro*

protease activity assay conducted on specimens taken from human patients in which ilomostat and alpha1-antitypsin (AAT) were added to the experimental samples that says nothing about the ototoxicity of ilomostat and AAT. Likewise, Lezdey et al. provides no information about the ototoxicity of agents for the treatment of otitis media. This is not persuasive because both Avidano et al. and Lezdey et al. teach the therapeutically effective amount of alpha-1 antitrypsin and these amounts are within Applicants' amounts set forth in claims 18 and 19. Therefore, both references not providing information of having ototoxicity in a patient is because it is most likely that significant ototoxicity did not occur. It is the Examiner's position that the above references suggest using the same effective amounts of the same compound as claimed by the Applicants. Applicants have not presented any evidence why Avidano et al's method as modified by Lezdey et al. for the treatment of otitis media and a perforated tympanic membrane with the same active agents with the same therapeutically effective amounts as claimed by Applicants would result in a different outcome (e.g. significant ototoxicity).

Applicants argue that a decrease in protease activity observed in an *in vitro* assay combined with a reported reduction of pain in a subject with swimmer's ear in Lezdey et al. neither teaches or suggests the treatment of otitis media "without significant ototoxicity" as recited in the currently pending claims. This is not found persuasive because Lezdey et al. teach a composition comprising alpha 1-antitrypsin and a steroid useful for the treatment of ear infections caused by pseudomonas while Avidano et al. teach that pseudomonas infection is involved in chronic otitis media

associated with nonintact tympanic membrane. Therefore, there is a reasonable expectation of success in treating patients suffering from otitis media and a perforated tympanic membrane caused by pseudomonas by administering effective amount of alpha 1-antitrpysin because Avidano et al. obtained statistically significant decrease in protease activity in sample collected from human with otitis media with composition comprising alpha-1 antitrypsin, and because Lezdey et al. teach the actual administration step of patients suffering from ear infections caused by pseudomonas with alpha-1-antitpryin. Applicants' claimed limitation of "without significant ototoxicity" is contemplated by both references not mentioning any reported significant ototoxicity with the utilized alpha-1-antiirpsin composition in both references as well as the employment of the therapeutically effective amount taught by the references within Applicants' amounts.

Applicants argue that it is well-established in the art that a perforated tympanic membrane contributes ototoxicity (Roland et al, Matz et al. both of record) and that Applicants discovery concerns the unexpected ability of alpha 1-antitrypsin to successfully treat otitis media "without significant ototoxicity" including ototoxicity associated with a perforated tympanic membrane. This is not persuasive because while a condition of having perforated membrane may contributes ototoxicity when untreated or lately diagnosed, it does not change the relevant teaching of Avidano et al. that alpha 1-antitrypsin composition effective for the treatment of otitis media with a perforated tympanic membrane. Therefore, upon the treatment of early diagnosed and prompt treatment with the alph-1 antitrypsin composition would inhibit progression of the

perforated tympanic membrane condition in a patient contributing to significant ototoxicity.

Applicants argue that given the clear evidence of such caution Roland et al. Matz et al, the cited art could not have provided a reasonable expectation that an effective, yet nonototoxic, dose of AAT could found that would permit successful treatment of otitis media in the setting of perforated tympanic membrane in the absence of significant ototoxicity. This is not persuasive because given that Avidano et al's data resulted in statistically significant decrease in protease activity in sample collected from human with otitis media with AAT composition, one would reasonably conclude that there would be a successful treatment of otitis media in the setting of perforated tympanic membrane in the absence of significant ototoxicity because underline condition that causes ototoxicity, i.e. perforated tympanic membrane would be effectively treated and significantly ameliorated.

Applicants argue that the citation of Brake et al. does not cure the deficiencies of the primary references. This is not persuasive because Brake et al. teach a method for producing AAT by recombinant methods from yeast providing high level production of the protein is well known in the art. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

In view of the above Office Action of July 9, 2007 is deemed proper and asserted with full force and repeated herein to obviate applicants' claims.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 5, 8, 11, 13 and 15-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) of record in view of Lezdey et al. (U.S.Patent No. 6,174,859 B1) of record.

Avidano et al. teach otorrhea samples were collected from **human patients with otitis media** and a **perforated tympanic membrane** and the samples were treated with ilomostat plus **alpha1-antitrypsin** in *vitro*. (abstract). A statistically significant ($p<0.05$) decrease in protease activity against **Pseudomonas** was seen **with the addition of alpha 1-antitrypsin** or **ilomostat plus alpha1-antitrypsin** but not with ilomostat alone. (see Fig. 1, page 348). Avidano et al. teach that chronic otitis media is a common problem associated with a nonintact tympanic membrane involving **pseudomonas**. (abstract). Avidano et al. teach that the concentration of ilomostat was prepared with 800ug/ml (0.8mg/ml) in a vehicle and the alpha 1-antitrypsin was prepared at a concentration of 100ug/ml (0.1mg/ml). These amounts are within the nontoxic amounts claimed by the Applicants set forth in claims 18 and 19.

Avidano et al. do not teach the actual *vivo* treatment with an effective *vivo* amount set forth in claim 13 and further comprising steroid set forth in claim 5.

Lezdey et al. teaches composition comprising **alpha 1-antitrypsin** and **steroid** compound for the **patients (vivo)** suffering from **ear infections** caused by

pseudomonas. (abstract, claims 1-16, particularly claims 1-3 and 16, Examples 1-8 particularly 7 and 8). Lezdey et al. teaches the effective amount of alpha 1-antitrypsin to be administered in vivo from about **0.1 to 20 mg per 1ml of solution**.

It would have been obvious to one of ordinary skill in the art to employ the teaching of Avidano et al. to a patient (vivo) suffering form otitis media and a perforated tympanic membrane by administering effective amount of alpha one-antitrypsin without significant ototoxicity because Avidano et al. obtained statistically significant decrease in protease activity against Pseudomonas in the sample collected from human who actually had otitis media and because the effective therapeutic amount of alpha one-antitrypsin for the treatment of ear infection caused by pseudomonas is well known by Lezdey et al. One would have been motivated to employ the successful teaching of Avidano et al. in vitro data comprising human sample of otitis media having perforated tympanic membrane to a patient actually suffering from such condition in order to achieve an expected benefit of actual effect in vivo. One would have been motivated to make such modification because Avidano et al. obtained statistically significant decrease in protease activity in sample collected from human with otitis media. Further, to employ the result obtained from the actual human sample taught by Avidano et al. and modify further in vivo would be next logical step. Moreover, to further incorporate an effective amount of steroid in the obvious method, such is obvious because Lezdey et al. teaches that steroids are routinely combined with **alpha 1-antitrypsin** for the **patients (vivo)** suffering from **ear infections** caused by **pseudomonas**. One would have been motivated to combine steroid with alpha one-antitrypsin in order to achieve at

least an additive effect in treatment of ear injection involved with pseudomonas with the routine combination therapy well known by Lezdey et al. With regard to the cause of perforated tympanic membrane due to tympanostomy set forth in claim 8, such is obvious because the alpha one-antitrypsin is effective for the treatment of otitis media with perforated tympanic membrane regardless of its etiology. Absent any evidence to contrary, there would have been a reasonable expectation of successfully treating an individual having otitis media and a perforated tympanic membrane with alpha one-antitrypsin well known by Avidano et al. having significant antiprotease activity in human otitis media sample.

Claims 14, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Avidano et al. (Head and Neck Surgery, Oct., 1998) of record in view of Lezdey et al. (U.S.Patent No. 6,174,859 B1) of record as applied to claims 5, 8, 11 and 13 above, and further in view of Brake et al. (U.S.Patent No. 4,752,576) of record.

The teachings of Avidano et al, Lezdey et al as applied as before.

Avidano et al, and Lezdey et al. do not teach the source of the alpha-1 antitrypsin is yeast-expressed rAAT set forth in claim 14 and the result of the treatment set forth in claims 20 and 21.

Brake et al. teach a method for producing alpha1-antitrypsin (AAT) by recombinant methods from yeast. This method provides high level production of the protein. (abstract, column 1, lines 59-68, column 2, lines 7-15).

It would have been obvious to one of ordinary skill in the art to employ the recombinant AAT obtained by yeast –expressed rAAT in Avidano et al as modified by

Lezdey et al. because Brake et al. teach the method of producing alpha1-antitrypsin (ATT) by recombinant methods in yeast provides high level production of the protein. One would have been motivated to employ yeast-expressed rAAT in Avidano et al's method modified by Lezdey et al. because the method of producing the alpha1-antitrypsin by yeast method provided high level of production and is well known and readily available by Brake et al. Further, to optimize different signs and symptoms to measure and detect an ototoxicity of a given treatment involving otitis media is well within the knowledge of the skilled artisan. Once the patient is being treated with a particular therapy involving a particular regimen, it is well within the knowledge of skilled artisan to routinely measure and evaluate the patient's condition and detect signs and symptoms of toxicity.

Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Kim/
Primary Examiner, Art Unit 1617

Jmk
April 1, 2008